REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As correctly stated in the Office Action Summary, claims 1-18 and 20-22 were pending in this application when last examined. Claims 21-22 stand withdrawn. Claims 1-18 and 20 stand rejected.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-8, 11 and 14-18 (as well as non-elected claim 21) remain rejected under 35 U.S.C. § 112, first paragraph, as purportedly lacking enablement. While the Office Action states that the specification is enabling for the treatment of viral encephalitis by administering "antibodies that bind the alpha-4 subunit of VLA-4" and "peptides of SEQ ID NOS: 3-5", the specification purportedly fails to provide enabling disclosure for other agents that inhibit the binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin. The Office Action has also maintained the assertion that Applicants are attempting to improperly incorporate by reference essential subject matter from non-U.S. patents. Specifically, the Office Action states that reliance upon the disclosure of other agents and peptides disclosed in WO 96/22966, WO 96/20216, WO 96/00581, and WO 96/06108 constitutes "essential subject matter." Applicants traverse.

First, Applicants note that the Examiner has acknowledged that peptides of SEQ ID NOS: 3-5 are enabled by the specification, and to this end, Applicants submitted claim 22

directed to agents comprising peptides of SEQ ID NOS: 3-5. However, the Examiner has withdrawn this claim from consideration as directed to a non-elected invention. Thus, although the Examiner suggests that Applicants amend the claims to recite peptides of SEQ ID NO: 3-5, Applicants submit that they have already attempted to comply with this request.

Turning to the rejection, Applicants submit that the specification does provide sufficient guidance to the skilled artisan as to how to locate and screen for appropriate agents with the ability to inhibit the binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement. These factors include, but are not limited to the breadth of the claims; the nature of the invention; the state of the art and the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.*, 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407.

To this end, Applicants submit that the present invention satisfies many of the above factors. The specification discloses many agents, including peptides, small molecules and antibodies, all of which inhibit binding of leukocytes to brain endothelial cells via leukocyte

surface antigen alpha-4 integrin. Pages 9 and 12 of the specification disclose antibodies that bind the alpha-4 subunit of VLA-4, page 13 discloses fragments to these antibodies, and pages 9 and 10 describe peptides with binding affinity for VLA-4, including peptides comprising SEQ ID NOs: 3-5.

The specification further discloses methods and assays to screen therapeutic agents for the binding specificity and/or the capacity to block the interaction of VLA-4 receptor with inflamed endothelial cells, other cells bearing a VCAM-1 counterreceptor, or purified VCAM-1 counterreceptor. In addition, the specification discloses how to obtain binding agents by producing and screening such agents for their ability to inhibit leukocytes bearing VLA-4 from binding to CNS endothelial cells. (*see* specification, pages 9-10 and page15, line 14 to page 16, line 4). The specification also discloses that libraries of compounds can be screened for specific binding to the alpha-4 integrin subunit of VLA-4 or to VCAM-1, optionally in competition with a reference compound known to have blocking activity. These methods and assays were well within the purview of one of skill in the art at the time of the claimed invention, and would not require undue experimentation to perform.

With regard to the skill in the art and prior art, Applicants submit that the skilled artisan would be able to make and use the present invention using what is known in the art combined with what is disclosed in the specification. Specifically, methods and assays for screening compounds, assays for determining binding affinity and the use of chemical libraries are well known in the art. The teachings and examples of the specification, in combination with the level of skill in the art, provide sufficient enablement for the current claims. Thus, for at least these reasons, Applicants respectfully request the withdrawal of this

rejection.

Furthermore, the Examiner maintains that improperly Applicants rely upon the disclosure of peptides disclosed in WO 96/22966, WO 96/20216, WO 96/00581, and WO 96/06108, as well as, U.S. Patent No. 5,510,332. *See* March 11, 2003, Official Action, Item 4, and that the teachings of these publications cannot be incorporated by reference, as they disclose essential subject matter.

Applicants again traverse this position. Applicants note that the claimed invention is directed to the use of such agents in treating viral encephalitis, and is sufficiently enabled by the specification as-filed, as discussed above. Therefore, the identity of a specific agent is not essential subject matter. Therefore, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102(e)

Claims 1-2, 4-8, 11, 16, 18, and 20 stand rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Thorsett et al. (U.S. Patent No. 6,001,809) in further evidence of *The Merck Manual of Diagnosis and Therapeutics* (16th Edition edited by Berkow et al., Merck Research Laboratories, Rahway, New Jersey, 1992, pages 1472-1474).

Thorsett et al. is cited for purportedly disclosing methods of treating viral encephalitis with inhibitors of VLA-4, including selecting for oligopeptides that block VLA-4 mediated adhesion, wherein the oligopeptides are selected via sequence analysis with antibodies that inhibit VLA-4 binding to VCAM-1. The Examiner states that Thorsett et al. is cited herein under 35 U.S.C. § 102(e) because this reference anticipates the broad claims encompassing "agents". The *Merck Manual* is cited for purportedly disclosing that viral encephalitis is

caused by arboviruses, polioviruses, echoviruses, coxsackieviruses, and herpes simplex. Therefore, the Examiner argues that the skilled artisan would have immediately envisaged herpes virus or arbovirus as the source of viral infection of viral encephalitis.

A rejection under 35 U.S.C. § 102 has been held to be proper when the extra references are cited to: (A) Prove the primary reference contains an "enabled disclosure; (B) explain the meaning of a term used in the primary reference; or (C) show that a characteristic not disclosed in the reference is inherent. M.P.E.P. § 2131.01. The secondary reference cited in the outstanding Office Action (*The Merck Manual of Diagnosis and Therapeutics*) does not fall into any of these three categories. Nor does the Office Action provide an explanation of which of the above categories applies to the *The Merck Manual.* The Office Action merely states that the secondary reference is purportedly cited to show that viral encephalitis is caused by arboviruses, polioviruses, echoviruses, coxsackieviruses, and herpes simplex . However, the Office Action does not explain why the secondary reference is appropriate under 35 U.S.C. § 102(e). Accordingly, as a proper *prima facie* rejection has not been adduced under § 102(e), Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

Without ceding that the two cited references are properly combined under 35 U.S.C. § 102(e) , Applicants submit that the cited references fail to recite every element of the presently claimed invention. To anticipate a claim, a single prior art reference must teach each and every element of the claimed invention. *See* M.P.E.P. § 2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); *Hybritech Inc.v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90

(Fed. Cir. 1986). The present invention is directed to a method of treating viral encephalitis in a patient, comprising administering to the patient an effective amount of an agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin. The patient is free of multiple sclerosis. Neither of the cited references discloses the claimed methods. Neither reference discloses that the patient receiving the claimed agents is free of multiple sclerosis.

Thus, in light of the above comments, Applicants request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-18 and 20 stand rejection under 35 U.S.C. § 103(a) as purportedly unpatentable over Thorsett et al. (U.S. Patent No. 6,001,809) in view of *The Merck Manual of Diagnosis and Therapeutics*, 16th Edition edited by Berkow et al., Merck Research Laboratories, Rahway, New Jersey, 1992, pages 1472-1474) and Bendig et al. (U.S. Patent No. 5,840,299) and/or Yednock et al. (U.S. Patent No. 6,033,665).

Thorsett et al. is cited for purportedly disclosing methods of treating viral encephalitis with inhibitors of VLA-4, including selecting for oligopeptides that block VLA-4 mediated adhesion. The *Merck Manual* is cited as reciting the diagnosis, etiology, pathology, prognosis and treatment of viral encephalitis and aseptic meningitis. Bendig et al. is cited for purportedly disclosing the use of inhibitory VLA-4α-specific antibodies, including humanized antibodies and the 21.6 antibody, to treat encephalitis. Yednock et al. purportedly

disclose the use of inhibitory VLA-4α-specific antibodies, including humanized antibodies and the 21.6 antibody to treat brain inflammation.

The Office Action states that that it would have been obvious to the skilled artisan to substitute inhibitory VLA-4α-specific antibodies in the treatment of viral encephalitis, given the same properties of the referenced VLA-4α-specific antibodies and VLA-4α-specific peptides, and the same therapeutic endpoints of inhibiting inflammatory responses. Applicants respectfully traverse.

As set forth in M.P.E.P § 2142, in order to establish a *prima facie* case of obviousness, three criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings: (2) there must be a reasonable expectation of success; and (3) the prior art references must teach or suggest all the claim limitations. As previously argued, the cited references fail to meet these requirements.

The present invention is directed to a method of treating viral encephalitis in a patient, comprising administering to the patient an effective amount of an agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin. The patient is free of multiple sclerosis.

The cited references fail to provide at least the requisite suggestion/motivation to either modify and/or combine the reference teachings to arrive at the claimed invention. Applicants note that none of the cited references disclose the treatment of viral encephalitis. Thorsett et al. merely disclose the treatment of inflammatory diseases using peptides. Bendig

disclose the use of VLA-α4-specific antibodies in the treatment of multiple sclerosis (MS), rather than a method of treating viral encephalitis infected patients that are free of MS using agents to inhibit the binding of leukocytes to brain endothelial cells via the leukocyte cell surface antigen alpha-4 integrin, as claimed herein. Yednock disclose brain inflammation, but fail to disclose or suggest the treatment of viral encephalitis.

Applicants submit that the etiologies and pathologies of viral encephalitis and meningitis, as well as those of viral encephalitis and MS are very different. These differences are such that one skilled in the art would not believe that treatment of one condition would correspondingly treat the other, or that the above conditions were correlative. Without this correlation, or any indication of predictability in this regard, there is no reasonable expectation of success in combining and/or modifying the references to arrive at the claimed invention.

At best, the rejection is based on the "obvious to try" standard . However, it is well established that in moving from the prior art to the claimed invention, one cannot base a determination of obviousness on what one of ordinary skill in the art might try or find obvious to try. *In re O'Farrel*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Instead, the proper test requires determining what the prior art would have led the skilled artisan to do. As discussed above, the cited references, alone or in combination, do not lead the skilled artisan to arrive at the claimed invention.

Applicants further submit that unexpected results are in fact present. It is a well established legal precedent that the presence of an unexpected, advantageous or superior result is evidence of nonobviousness. See M.P.E.P. § 716.02(a); *In re Papesch*, 315 F.2d

381, 137 U.S.P.Q. 43 (C.C.P.A. 1963). Along these lines, it is also well established that "a greater than expected result" is evidence of nonobviousness. *See* M.P.E.P. § 716.02(a); *In re Corkill*, 711 F.2d 1496, 226 U.S.P.Q. 1005 (Fed. Cir. 1985).

In the case of the present invention, the agents unexpectedly did not cause an increase in viral load. The agents of the present invention are meant to treat and/or prevent viral encephalitis in a subject. However, the agents of the present invention are able to treat encephalitis caused by a virus without affecting viral load, *i.e.*, without making the infection worse. An increase in viral load is an expected outcome of inhibiting immune cell entry into the brain, and the skilled artisan would expect that these agents would also result in an increase in viral load in the subject upon administration. Unexpectedly, the agents of the present invention protected the animal model from viral encephalitis and fails to cause an increase in viral load. Thus, any *prima facie* case of obviousness based on the cited references is rebutted by such unexpected results.

In light of the above, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

In the event any further fees are due to maintain pendency of this application, the Examiner is authorized to charge such fees to Deposit Account No. 02-4800.

Respectfully submitted,

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